Remarks

Reconsideration of this Application is respectfully requested.

I. Status of the Claims

Upon entry of the foregoing amendment, claims 77-80 and 82-98 are pending in the application, with claims 77 and 94 being the independent claims. Claims 81 and 99-106 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein.

Claims 77 and 94 are sought to be amended. Support for the amendment to claim 77 can be found, *inter alia*, in the specification at page 6, lines 11-12 and at page 9, line 12, through page 10, line 3. Support for the amendment to claim 94 can be found, *inter alia*, in the specification at page 9, line 12, through page 10, line 3. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Rejection of Claims 104 and 105 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 104 and 105 under 35 U.S.C. § 102(b) as allegedly being anticipated by PCT Appl. Pub. No. WO 99/25359 to Karlsson *et al.* (Office Action, page 3, lines 16-17). Applicants respectfully traverse the rejection.

However, in furtherance of prosecution, Applicants have cancelled claims 104 and 105. Therefore, as the rejection of claims 104 and 105 under 35 U.S.C. § 102(b) has been rendered moot, Applicants respectfully request that the rejection be withdrawn.

III. Rejection of Claims 77-80 and 82-98 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 77-80 and 82-98 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,187,765 B1 to Harris *et al.* (hereinafter "Harris"). (Office Action, page 5, lines 4-5). Applicants respectfully traverse the rejection.

This application attempts to solve the problems associated with the U.S. Food and Drug Administration requirement that all nebulizer suspensions must be sterile (see specification, page 1, lines 4-6). The problems associated with sterilizing suspensions include the following: components of the formulation being destroyed by heat sterilization, alteration in particle size by end sterilization, unsuitability of filtration due to the particle size being significantly greater than the filter pore size, and components of the formulation being destroyed by gamma radiation sterilization (for example, budesonide)(see specification, page 1, line 20, through page 2, line 10) .

The present invention is directed to a method for preparing a sterile pharmaceutical composition of a steroid comprising: (i) dissolving a non-sterile steroid in a solvent to yield a solution of the steroid, (ii) filtering the solution to yield a sterile solution, (iii) combining the sterile solution with sterile water to form a suspension, (iv) optionally removing all or part of the solvent, (v) treating the sterile suspension of (iii) or (iv) to obtain a particle size distribution having a mass median diameter less than 10 μm,

(vi) under sterile conditions combining the suspension with a pharmaceutically acceptable carrier to yield a sterile pharmaceutical composition comprising a suspension of the steroid having a mass median diameter less than 10 μm, and (vii) storing the sterile pharmaceutical composition in sterile containers.

Harris teaches an aqueous nebulizer suspension containing mometasone furoate monohydrate (Abstract) and describes the preparation of mometasone furoate monohydrate in Example 1 (column 6, lines 25-62). The steroid is dissolved in acetone to form a solution followed by filter sterilization (steps (1) and (2) of Example 1). The solution is heated and the elevated temperature is maintained while water is added progressively with stirring so that a precipitate forms (steps (3) to (7) of Example 1). The suspension is then cooled and the precipitate is filtered, washed, and dried in a vacuum oven to form powdered mometasone furoate monohydrate (steps (8) to (10) of Example 1). In Example 2 of Harris, the dried mometasone furoate monohydrate is combined with sterile solutions of excipients to form a suspension (steps (1) to (3) of Example 2) and the particle size is adjusted (step (4) of Example 2). Carrier is then added and the suspension is dispensed into sterile containers (steps (5) to (7) of Example 2).

Harris discloses a two stage process, the two stages separated by the drying step at the end of stage 1 (step (10) of Example 1). The mometasone furoate monohydrate produced in stage 1 is then re-suspended before the particle size of the steroid is adjusted (steps (1) to (4) of Example 2). Conversely, Applicants' claimed invention provides a single stage method for preparing a sterile pharmaceutical composition of a steroid. In Applicants' method the non-sterile steroid is dissolved in a solvent to form a solution and

the solution is sterilized by filtration. After filtration the steroid is converted into a suspension for further processing. Therefore, in Applicants' claimed method the suspension is not dried during preparation.

As Examples 1 and 2 of Harris provide the only detailed disclosure of the method of production of the claimed suspension, one of ordinary skill in the art would be directed to these examples. Harris discloses that the dried mometasone furoate should have a water content of 3.3 percent by weight and contain 96.7 percent by weight of mometasone furoate (Example 1, column 6, lines 59-62). Therefore, Example 1 of Harris teaches that all acetone should be removed in the vacuum oven of step (10). As acetone is a class 3 solvent, one of ordinary skill would understand from Harris that all class 3 or lower solvents must be entirely removed from the formulation. Thus, the mometasone furoate of step (10) is a dried intermediate product which must be dissolved in step (3) of Example 2.

This Harris drying step is omitted from Applicants' claimed method. In the present invention, the suspension of step (iii) or (iv) is treated in step (v) without forming a dried product. Thus, in the present invention, the solvent can be removed from the suspension but the steroid remains in a water-based suspension.

Harris does not provide a reason why one of ordinary skill in the art would use a single phase method or a reason why one would one would treat the suspension of (iii) or (iv) to reduce its particle size. Conversely, Harris teaches that the dried intermediate is dissolved in a sterile solution before it is further processed (Example 2, steps (1) to (3)).

Similarly, in *In re Freed*, 425 F.2d 785 (CCPA 1970) the claimed invention was a single-step process for producing calcium pantothenate whereas the prior art disclosed a

two-stage reaction. The court held that the single-step process was not obvious over the two-step process disclosed in the prior art. The court explained that

> it seems more logical and reasonable to infer that one teaching a chemical reaction process would set out the least number of reactions thought necessary to accomplish the desired objective. Thus, one skilled in the art who reads the teaching would have to presume that if the reactants were not combined in the manner shown, some adverse side reaction or no reaction at all would occur.

Id. at 788.

Therefore, Harris does not render obvious the claimed invention. Applicants respectfully request that the rejection of claims 77-80 and 82-98 under 35 U.S.C. § 103(a) as being unpatentable over Harris be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Stephanie Elmer

Stephanie L. Elmer
Attorney for Applicants
Registration No. 59,244

Date: 7/24/08

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

851556_1.DOC